Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1200674

J Med Palliat Care 2023; 4(1): 58-62

Prognostic factors for survival in pancreatic cancer patients received radiotherapy: a single-center experience

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Cite this article as: Alkış H. Prognostic factors for survival in pancreatic cancer patients received radiotherapy: a single-center experience. J Med Palliat Care 2023; 4(1): 58-62.

ABSTRACT

Aim: To investigate survival outcomes and factors affecting the prognosis of patients with pancreatic cancer (PC) who received radiotherapy (RT).

Material and Method: A total of 73 patients with PC who received RT between 2013 and 2021 were included in the study. Clinical, demographic, and histopathological features of the patients, and the goal of RT (adjuvant, definitive, neoadjuvant, or palliative) were recorded.

Results: Median age of the patients was 62 (37-78). Male to female ratio was 1.6. In patients treated with adjuvant (n=52), definitive (n=13), and palliative (n=7) RT, median overall survival (OS) was 25.7 (11.6-39.7), 16 (7-67), and 9 (5-52) months, respectively. Survival time of 1 patient who received neoadjuvant RT was 26.6 months. Lymph node ratio (LNR) was significantly associated with OS. Patients with LNR ≤0.4 had better survival compared to those with LNR >0.4 (p=0.003). Furthermore, patients with LNR ≤0.4 and received adjuvant RT survived longer than the rest of the patients (12.1 vs. 7.7 months, p=0.001). Larger tumors (p=0.04) and LNR (p=0.003) were associated with poorer survival in univariate analysis, however, in the multivariate analysis, OS was found significantly affected only by LNR (p=0.01). Other factors were not found associated with survival.

Conclusion: LNR had a strong correlation with OS in PC patients treated with radiation. Smaller LNR was associated with better survival in patients who received RT in the adjuvant setting.

Keywords: Pancreatic cancer, prognostic factors, survival, radiotherapy

INTRODUCTION

Pancreatic cancer (PC) is the fourth malignancy resulting in cancer-related death despite being relatively less common compared to other cancers (1). Smoking, advanced age, obesity, heavy alcohol consumption, chronic diabetes mellitus, and non-O blood group are among the etiological factors of PC (2-7). Patients with PC located in the body or tail of the pancreas have lower survival rates because of more advanced disease at the time of diagnosis compared to the ones with tumors in the head of pancreas (8, 9).

Components of treatment modality of PC are surgery, chemotherapy (CT), and radiotherapy (RT). Surgery plays major role in the management of PC, however, only 15 to 20% of the patients present with operable disease at the time of diagnosis (10, 11). Following optimal resection, important prognostic factors are resection margin status, lymph node involvement, tumor size and tumor grade (12-15). CT and RT may be applied in several phases of treatment according to tumor's resectability or status of metastasis. While RT is frequently administered in adjuvant setting with CT (16-19), definitive and neoadjuvant RT with CT are the options in locally unresectable PC and resectable/borderline resectable PC, respectively (20, 21). Palliative RT is an effective option to control pain or local symptoms due to obstruction caused by primary tumor or metastatic lesions (22, 23).

In this study, the aim was to investigate the factors affecting the survival outcomes of the patients diagnosed with PC and treated with RT either as a part of multimodal management or for palliation.

MATERIAL AND METHOD

A total of 73 patients (male: 45, female: 28) diagnosed with pancreatic adenocarcinoma and attended to the department of radiation oncology between 2013 and 2021 were included in the study. Patients' data were obtained from medical recordings. The study was approved by

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Received: 07.11.2022 **Accepted:** 31.01.2023

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the Marmara University Clinical Researches Ethics Committee (Date: 13.06.2022, Decision No: 09.2022.86) and conducted by principles of the Declaration of Helsinki. Staging was done according to AJCC (8th edition) staging system. Patients treated with neoadjuvant, adjuvant, definitive or palliative RT were recorded. Patients' characteristics are summarized in **Table 1**.

Table 1. Clinicopathologic features of the patients

Characteristics	Sex		Total % (n)	p value
	Male % (n)	Female % (n)		
Initial symptom				0.3
Weight loss	16 (7)	21 (6)	18 (13)	
Fatigue	24 (11)	14 (4)	20 (15)	
Pain	7 (3)	22 (6)	12 (9)	
Jaundice	42 (19)	25 (7)	36 (26)	
Other	11 (5)	18 (5)	14 (10)	
LNR				0.7
≤ 0.4	65 (29)	75 (21)	69 (50)	
> 0.4	4 (2)	7 (2)	5 (4)	
Unknown	31 (14)	18 (5)	26 (19)	
Blood groups				0.9
O	20 (9)	25 (7)	22 (16)	
A	44 (20)	42 (12)	44 (32)	
B	16 (7)	11 (3)	13 (10)	
AB	9 (4)	11 (3)	10 (7)	
Unknown	11(5)	11 (3)	11 (8)	
Tumor location				0.6
Head	76 (34)	79 (22)	77 (56)	
Body	11 (5)	14 (4)	12 (9)	
Tail	13 (6)	7 (2)	11 (8)	
Tumor stage				0.5
T1	9 (4)	3 (1)	7 (5)	
T2	45 (20)	36 (10)	41 (30)	
T3	42 (19)	61 (17)	49 (36)	
T4	4 (2)	-	3 (2)	
Nodal status				0.1
N0	9 (4)	21 (6)	14 (10)	
N1	45 (20)	32 (9)	40 (29)	
N2	13 (6)	29 (8)	19 (14)	
Nx	33 (15)	18 (5)	27 (20)	
Stage				0.8
I	47 (21)	54 (15)	49 (36)	
II	20 (9)	25 (7)	22 (16)	
III	22 (10)	18 (5)	21 (15)	
IV	11 (5)	3 (1)	8 (6)	
Grade				0.1
I	4 (2)	7 (2)	5 (4)	
II	45 (20)	57 (16)	49 (36)	
III	13 (6)	7 (2)	11 (8)	
Unknown	38 (17)	29 (8)	34 (25)	
CEA				0.5
< 5	44 (20)	36 (10)	41 (30)	
≥ 5	16 (7)	25 (7)	19 (14)	
Unknown	40 (18)	39 (11)	40 (29)	
CA 19-9				0.3
< 34	24 (11)	11 (3)	19 (14)	
≥ 34	38 (17)	50 (14)	43 (31)	
Unknown	38 (17)	39(11)	38 (28)	

LNR, lymph node ratio; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9

Initial diagnostic imaging was computed tomography in 30 patients, magnetic resonance imaging in 26, and positron emission tomography in 1 patient. Biopsy was performed in 16 patients who had unresectable or metastatic disease. Surgical procedure was distal pancreatectomy in 9 patients and Whipple procedure in 44 who underwent surgery and received adjuvant RT (n=53; 72%). Thirteen patients (18%) received definitive RT. Palliative RT was administered to 7 patients (9%) to control symptoms due to primary tumor and only one patient was treated with neoadjuvant RT (1%). Radiation fields encompassed tumor bed and regional nodes in adjuvant setting with a treatment dose of 45-50.4 Gray (Gy). In the neoadjuvant, definitive and palliative RT planning, only tumor was covered with median doses of 45, 50.4, and 30 Gy, respectively. Volumetric arc therapy was used for RT planning. Adjuvant CT regimen was gemcitabine based in 44 and fluorouracil (FU) based in 9 patients. In patients treated with adjuvant RT, concurrent CT regimens were capecitabine (n=28) and gemcitabine (n=25). For patients treated with definitive chemoradiation, gemcitabine and capecitabine were administered concomitantly in 6 and 7 patients, respectively. One patient treated with neoadjuvant chemoradiation received concurrent capecitabine.

Date of death or last follow-up time in surviving patients were recorded. Overall survival (OS) is defined as the time between the date of diagnosis and the date of death or last follow-up date of the patients.

Statistical Analyses

Statistical Package for Social Sciences (SPSS) for Windows 23.0 IBM SPSS Statistics, New York, USA was used for statistical analyses. Kaplan–Meier method, and the log-rank test was used for survival analysis. Univariate and multivariate Cox regression analyses were used to determine variables which were predictors of OS. All of the tests were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

Median age of the patients was 62 (37-78). Male to female ratio was 1.6. Median follow up time was 19.5 (3.3-102) months. In the patients received RT in the adjuvant setting, OS was significantly better than the rest of the study population (p=0.01). Median OS of the patients treated with adjuvant and non-adjuvant RT was 25.7 (11.6-39.7) and 17 (7.9-25.1) months, respectively (p=0.01). Median OS for patients treated with definitive (n=13) and palliative (n=7) RT was 16 (7-67) and 9 (5-52) months, respectively. Survival time of 1 patient received neoadjuvant RT was 26.6 months.

The results of univariate analyses for OS are shown in **Table 2**.

Table 2. Cox regression univariate analysis for overall survival

Variables	p value	Hazard rate	95% Confidence interval	
			Lower	Upper
Age (≤65 vs. >65)	0.25	1.369	0.798	2.348
Gender (Female vs. male)	0.34	0.766	0.443	1.323
Blood groups (0 vs. non-0)	0.23	1.487	0.775	2.854
Smoking (Smoker vs. no smoker)	0.57	1.047	1.273	3.102
Tumor location (Head vs. body-tail)	0.29	1.379	0.757	2.514
Tumor stage (T1-2 vs. T3-4)	0.04	1.755	1.023	3.012
Stage (I,II vs. III)	0.51	0.766	0.346	1.696
Grade (I,II vs. III,IV)	0.73	1.133	0.561	2.288
LNR (≤ 0.4 vs. >0.4)	0.003	5.103	1.711	15.220
Surgical margins (Negative vs. positive)	0.31	2.917	0.373	2.2823
CEA (<5 vs. ≥5)	0.81	1.038	0.771	1.316
CA19-9 (<34 vs. ≥34)	0.97	1.008	0.678	1.498
Adjuvant CT regimen (Gemcitabine vs. 5-Flourouracil/ capecitabine)	0.91	1.052	0.432	2.563

LNR, lymph node ratio; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; CT, chemotherapy

LNR (≤0.4 vs >0.4) was found associated with survival (p=0.003). Patients with LNR >0.4 had poorer OS compared to them with LNR ≤0.4 (**Figure 1**). Furthermore, in the subgroup analyses, patients with LNR ≤0.4 and received adjuvant RT survived longer than the rest of the patients (12.1 vs. 7.7 months, p=0.001). Additionally, advanced tumor stage (T3 and T4) was found associated with poorer survival (p=0.04) (**Figure 2**). However, in the multivariate analysis, only LNR was found significantly associated with OS in all study population (p= 0.01). Tumor grade, age, sex, tumor location, stage, blood group, smoking, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels was not associated with survival. Additionally, positive surgical margin was not significantly associated with survival in patients who underwent surgery.

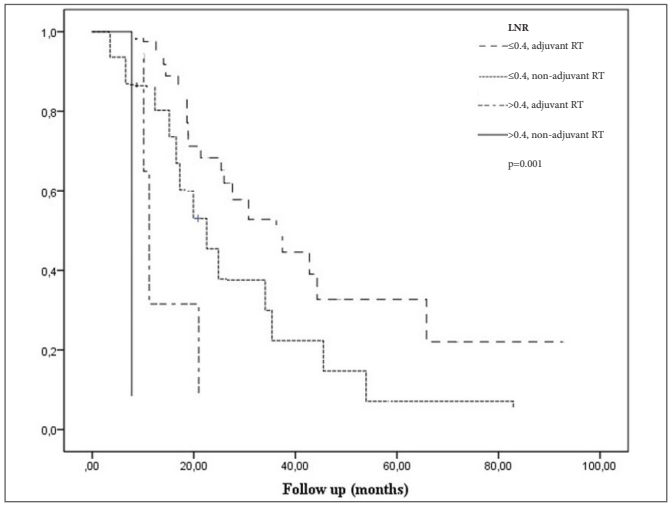

Figure 1. Association between lymph node ratio (LNR) and survival in patients treated with adjuvant and non-adjuvant radiotherapy

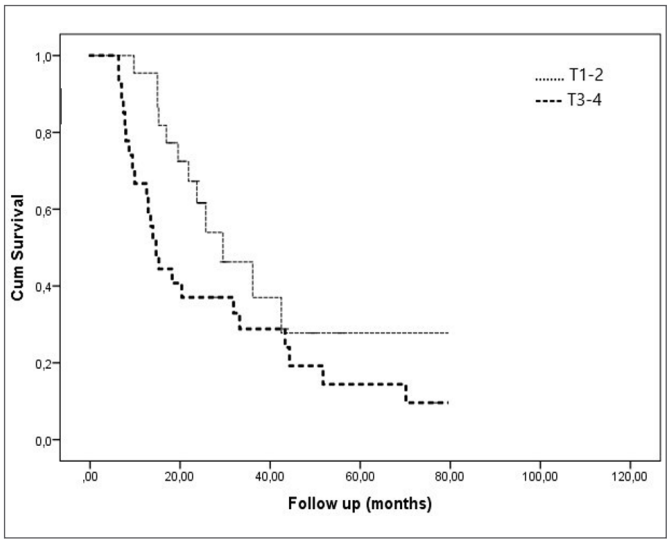

Figure 2. Association between tumor stage and survival

DISCUSSION

Pancreatic cancer is a relatively less common malignancy, however, has a worse prognosis and higher mortality compared to the other cancers (1). Several factors such as smoking, heavy alcohol use, non-O blood group, and advanced age are blamed for the etiology of PC (2-7). A two-fold increased risk of PC is reported with smoking (3). PC is more frequent in Western and industrialized countries which may be related to increased obesity and/ or higher numbers of people at advanced age (24). In this study, 51% of the patients was smokers and approximately half of the patients were at advanced age (46%). Majority of the patients was with non-O blood group (71%).

Routine screening for PC is not clearly established. Preoperative CA 19-9 levels may be useful in detecting PC, however, while CA 19-9 may increase in diseases/ disorders related to pancreaticobiliary ducts, pancreatitis or poorly controlled diabetes, it is generally used to monitor the response to therapy or detect recurrences (25). In this study, preoperative CA 19-9 levels were increased in only one-third of the patients who had available data.

Although surgery is the cornerstone of the PC treatment and optimal resection of the tumor has prognostic importance, only 15 to 20% of the patients have resectable tumors when diagnosed with PC (10, 11). In operable PC, clear resection margin is an important prognostic factor and patients with R0 resection margins have a better prognosis compared to those with R1 or R2 resection margins (26). Nevertheless, 5-year and 10-year OS rates are reported as 25% and <10%, respectively, even for patients resected with clear margins (27). In this study, survival rate of the patients with resectable PC was better than the rest of the study population as expected. However, in contrast to the previous studies, resection margin status was not found significantly associated with survival.

Radiotherapy may be applied with chemotherapy as a part of multimodal management or for palliation in PC. Neoadjuvant chemoradiation is an option in resectable and borderline resectable PC. Results of PREOPANC-1 trial, the first large phase III randomized trial, showed that neoadjuvant chemoradiation improved survival in patients with resectable or borderline resectable PC in addition to higher rates of clear resection margins (20). However, in this study, only one patient was referred for neoadjuvant management and treated with neoadjuvant chemoradiation. Locally unresectable or metastatic disease at the time of diagnosis is commonly seen in PC patients. Definitive RT with CT is an option in patients who are not suitable for surgery and generally recommended after 4-6 cycles of systemic CT. In GERCOR study, definitive RT with concurrent CT was reported to be superior to CT alone in management of non-metastatic locally unresectable pancreatic cancer (21). In this study, definitive RT was administered to one fifth of the patients and did not significantly affect survival compared to the remaining of the patients. Location of the primary tumor may cause severe symptoms. Tumors at the head of pancreas which is the most common localization of PC usually present with obstructive jaundice. Additionally, pain due to celiac plexus involvement or duodenal invasion may be observed in PC patients (28). In this study, majority of the tumors (77%) were located at the head of pancreas with a jaundice rate of 36%. Tumor related symptoms (i.e pain, biliary obstruction, or gastric outlet/duodenal obstruction) may be palliated with RT. Particularly, RT has a strong effect on pain relief derived from primary tumor in nonresponders to effective medical therapy and/or interventional procedures (22, 23). In this study, 10% of the patients needed palliation for symptoms due to primary tumor's complications.

In postoperative PC patients, lymph node involvement has a great importance in addition to clear surgical margins for predicting prognosis of the disease. Asiyanbola et al. (29) reported that LNR which is the ratio of involved lymph nodes to resected lymph nodes is an independent and most significant factor in predicting survival. They found a cutoff value of 0.4 for prediction of survival. LNR >0.4 has been reported to be associated with poor OS and high risk of local failure. In this study, the same cutoff value was used and the patients were grouped as LNR >0.4 and ≤0.4, and in consistent with Asiyanbola et al.'s study, LNR >0.4 was found strongly correlated with poorer survival (Fig. 1). Size, grade and location of the tumor also have prognostic importance for PC; larger tumor sizes are associated with shorter survival (15). Tumors located in the body or tail of the pancreas are associated with lower survival rates because of more advanced disease at the time of diagnosis (8, 9). In this study, larger tumor sizes were found associated with poorer survival by univariate analysis. However, a statistically significance for OS was not found by multivariate analysis. Additionally, majority of the tumors were located at the head of pancreas, but tumor location did not significantly affect survival of the patients. Although tumor grade is also associated with prognosis and survival of PC (30), an improved survival with lower tumor grade was not found.

Impact of multimodal treatment on disease control after maximal resection of primary tumor was shown by previous studies which demonstrated that addition of postoperative CT and RT improved survival when compared to surgery alone (16-19). Although this study does not have a homogeneous treatment population, patients treated with adjuvant RT and CT established better survival. Additionally, OS was significantly better in patients with smaller LNR and treated with adjuvant RT when compared to them received RT in non-adjuvant setting. This finding may be explained by an extra contribution of adjuvant radiation to survival in patients with less involved lymph nodes.

The study has some limitations. It is a retrospective study and despite the collection of nine years of data, it has small number of patients.

CONCLUSION

Patients with PC had poor prognosis and LNR had a strong correlation with OS in patients treated with radiation. Moreover, smaller LNR was associated with better survival in patients who received RT in the adjuvant setting.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Marmara University Clinical Researches Ethics Committee (Date: 23.06.2022, Decision No: 09.2022.86).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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